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Influence of acyl groups on glucopyranoside reactivity in Lewis acid promoted anomerisation

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ABSTRACT

Lewis acid promoted anomerisation has potential in *O*- or *S*-glycoside synthesis. Herein, the anomerisation kinetics of thirty-one β-D-glucopyranosides was determined to determine how particular acyl protecting groups and their location influence reactivity towards a Lewis acid promoted reaction. The replacement of acetyl groups with benzoyl groups led to reduced reactivity when located at O-3, O-4 and O-6. However a reactivity increase was observed when the acetyl group was replaced by a benzoyl group at O-2. The 2,3,4,6-tetra-*O*-(4-methoxy)benzoate had an ~2-fold increase in rate when compared to the tetrabenzoate.

Introduction

Reactions at the anomeric centre are influenced by a variety of factors. For instance, in glycosylation, protecting groups on saccharide hydroxyl groups influence the stereochemical outcome as well as the reaction rate.[1] Differences in glycosylation rate can be exploited in reactivity based oligosaccharide synthesis in one pot.[2] Acyl protecting groups are considered 'disarming' in such glycosylation reactions when compared to benzyl protecting groups.[3] This is because the acyl group is more electron withdrawing than the ether and reduces the stability of transition states leading to cationic intermediates[4] resulting from exocyclic cleavage in these reactions.

Reactivity in Lewis acid promoted anomerisation[5–7] is also influenced by protecting groups.[8,9] The reaction is believed to proceed *via* a cationic intermediate resulting from endocyclic cleavage[10,11] (Scheme 1). Acyl groups located on the saccharide oxygen atoms reduce the rate of these reactions compared to when methyl groups are present.[6,8] Furthermore, there are differences between acyl groups. Tetra-*O*-benzoyl-β-D-glucopyranoside **2β** is more reactive than the corresponding tetraacetate **1β**. Based on inductive effects the presence of benzoyl groups would destabilize a cationic intermediate more than acetyl groups. However, the use of benzoylated reactants has been more successful, giving higher yields and shorter reaction times in equatorial to axial anomerisation reactions compared to reactions of the analogous acetylated reactants. This has been demonstrated in glycosphingolipid synthesis achieved *via* Lewis acid promoted anomerisation,[12,13] and more recently in the successful anomerisation of benzoylated glycosyl thiols.[14]

In this paper the influence of acyl groups on the reactivity of a Lewis acid promoted anomerisation reaction of a series of *O*-glucopyranosides is probed further with a view to identification of protecting group strategies that would lead to wider application of anomerisation.[15–22] A variety of acyl protected glucopyranosides are prepared and a structure reactivity relationship is established. Here we report that the presence of benzoyl groups at C-2 of the β-glucopyranoside generally leads to a rate enhancement in the anomerisation reaction, while benzoyl groups at C-3, 4 or 6 lead to a rate reduction when compared to the presence of acetyl groups at these positions. However, the replacement of all four acetyl groups with benzoyl groups gave the highest reactivity. Other tetra-*O*-acyl derivatives with improved reactivity compared to tetra-*O*-benzoyl derivatives are also reported.

Results and discussion

Synthesis of compounds for study

The preparation of monobenzoylated compounds was first investigated (Scheme 2). Thus Zemplén deacetylation of **1β**, which

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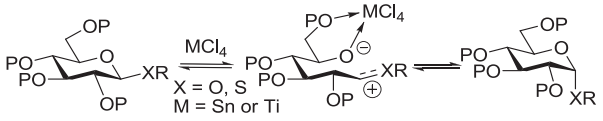
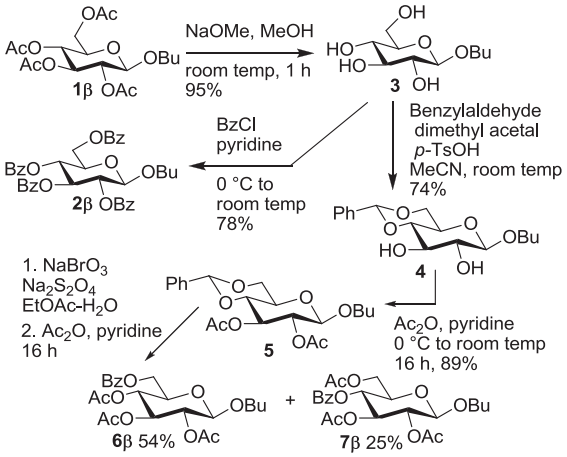


Scheme 1. Proposed mechanism for the Lewis acid promoted anomerisation of glucopyranosides.



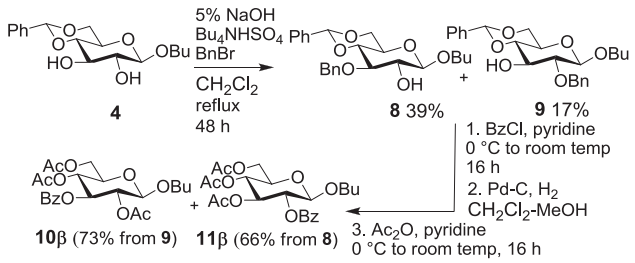
Scheme 2. Synthesis of **6β** and **7β**.

has been described previously,[7] gave **3**. Reaction of **3** with benzaldehyde dimethyl acetal in the presence of *p*-TsOH gave **4**. Acetylation gave **5**. Oxidative cleavage of the benzylidene group using $NaBrO_3$-$Na_2S_2O_4$ under bi-phasic conditions, followed by acetylation, resulted in the formation of a separable mixture, giving **6β** (54%) and **7β** (25%). The application of biphasic $NaBrO_3$-$Na_2S_2O_4$, described by Adinolfi and co-workers,[23] was used frequently herein for the successful removal of benzyl groups as well as partial oxidative cleavage of benzylidene groups.

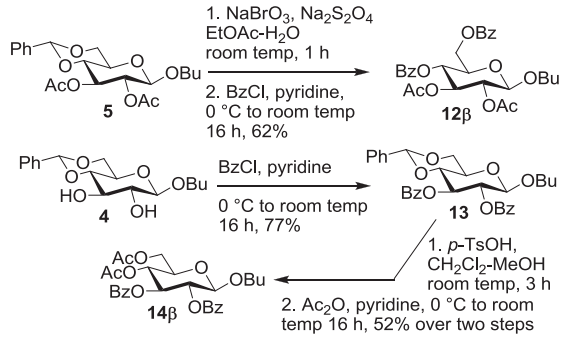
Next the benzylation of **4** (Scheme 3) under the biphasic alkali conditions previously reported by Garegg and co-workers[24] gave a mixture of **8** and **9** which were isolated in 39% and 17% yields, respectively. Benzoylation, followed by catalytic hydrogenolysis and subsequent acetylation gave **10β** and **11β** in 73% and 66% yields, respectively, over the three steps from **8** and **9**.

Attention turned to the preparation of compounds with two or three benzoate groups (Schemes 4–6). Partial oxidative cleavage of **5** and subsequent benzoylation gave **12β** (62%). Benzoylation of **4** was followed by acid catalysed cleavage of the benzylidene acetal in CH_2Cl_2-MeOH and acetylation to give **14β**.

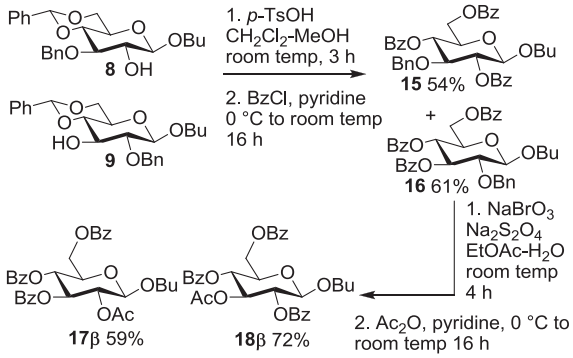
Acid catalysed cleavage of the benzylidene group from both **8** and **9** and their subsequent benzoylation gave **15** and **16**. Oxidative removal of the benzyl groups with $NaBrO_3$-$Na_2S_2O_4$ proceeded smoothly and subsequent acetylation gave **17β** and **18β**.



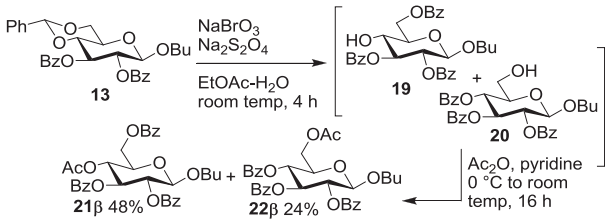
Scheme 3. Synthesis of **10β** and **11β**.



Scheme 4. Synthesis of **12β** and **14β**.



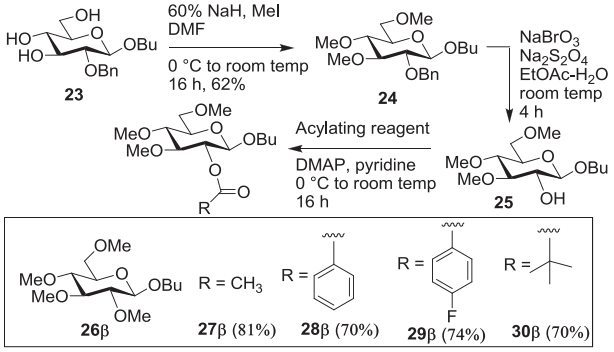
Scheme 5. Synthesis of **17β** and **18β**.



Scheme 6. Synthesis of **21β** and **22β**.

Partial oxidative cleavage of the benzylidene group of **13** gave a mixture of **19** and **20**. Subsequent acetylation gave **21β** and **22β**.

Intermediate **23**, prepared from **9** (Scheme 7), was treated with NaH and methyl iodide to give **24**. The benzyl group of **24** was then removed to give **25**. Acylation of **25** gave **27β**–**30β**. The tetra-*O*-methyl derivative **26β** was prepared as previously described.[8]



Scheme 7. Synthesis of **27β**–**30β**.